Mortality in US Army Gulf War Veterans Exposed to 1991 Khamisiyah Chemical Munitions Destruction

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Objectives. We investigated whether US Army Gulf War veterans who were potentially exposed to nerve agents during the March 1991 weapons demolitions at Khamisiyah, Iraq, are at increased risk of cause-specific mortality.

Methods. The cause-specific mortality of 100 487 exposed US Army Gulf War veterans was compared with that of 224 980 unexposed US Army Gulf War veterans. Exposure was determined with the Department of Defense 2000 plume model. Relative risk estimates were derived from Cox proportional hazards models.

Results. The risks of most disease-related mortality were similar for exposed and unexposed veterans. However, exposed veterans had an increased risk of brain cancer deaths (relative risk [RR] = 1.94; 95% confidence interval [CI] = 1.12, 3.34). The risk of brain cancer death was larger among those exposed 2 or more days than those exposed 1 day when both were compared separately to all unexposed veterans (RR = 3.26; 95% CI = 1.33, 7.96; RR = 1.72; 95% CI = 0.95,3.10, respectively).

Conclusions. Exposure to chemical munitions at Khamisiyah may be associated with an increased risk of brain cancer death. Additional research is required to confirm this finding. (*Am J Public Health.* 2005;95:1382–1388. doi:10.2105/AJPH.2004.045799)

On March 4 and 10, 1991, combat engineer and explosive ordnance disposal units of the US Army XVIII Corps destroyed 2 large Iraqi weapons caches at Khamisiyah, Iraq. In October 1991, March 1992, May 1992, and May 1998, representatives from the United Nations Special Commission inspected Khamisiyah and detected the existence of sarin and cyclosarin in both intact and damaged rockets in the bunker and pit. Military personnel who were possibly exposed to chemical warfare agents at Khamisiyah were identified by environmental and climatological modeling of the plume dispersion.

Sarin is a toxic nerve agent produced for chemical warfare. Sarin can be inhaled or absorbed via the mucous membranes, skin, or eyes, and at sufficient dosage it can cause convulsions and death.[1] Acute sarin exposure produces a well-characterized acute cholinergic reaction, and doses sufficient to produce an acute reaction have been associated with persistent health effects such as fatigue, vision problems, and headaches.[1] There is no evidence that sarin is carcinogenic.[2]

Several studies have examined cause-specific mortality risks associated with Gulf War service by comparing the mortality of all Gulf War veterans to that of veterans who served in the military during the period of the Gulf War but did not serve in the Persian Gulf region.[3–5] Although reporting that Gulf War veterans were at increased risk for traumatic deaths, the studies did not find any increased risk of disease-related deaths. One of these studies assessed cause-specific mortality among Gulf War veterans who were considered exposed to nerve gas on the basis of the 1997 plume model.[4] When the mortality of 48 281 Gulf War veterans who were exposed to nerve gas at Khamisiyah was compared with that of 573 621 Gulf War veterans who were not exposed, there was no increased risk in either overall or cause-specific mortality among exposed veterans. Another study using the same exposure model found no unusual morbidity among exposed troops.[6]

To determine whether adverse health are outcomes associated with exposure to chemical agents released at Khamisiyah, we compared the mortality of all exposed US Army Gulf War veterans to that of unexposed US Army Gulf War veterans, using the 2000 plume model to assess potential for exposure.

METHODS

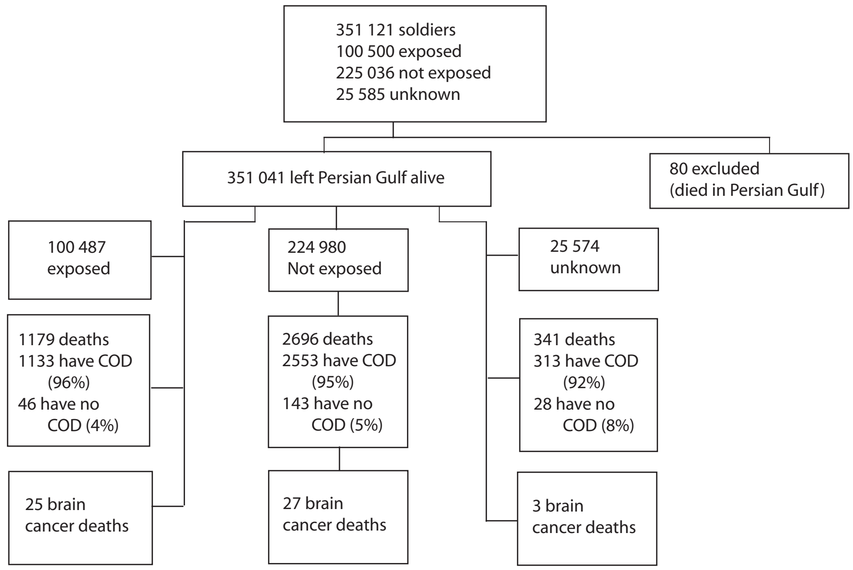
Identification of Study Subjects

The cohort for this study was selected in collaboration with the Office of the Special Assistant for Gulf War Illnesses, the Deployment Environmental Surveillance Program of the US Army Center for Health Promotion and Preventive Medicine, and the Environmental Epidemiology Service of the Department of Veterans Affairs.

We used the 2000 plume model to provide exposure status for 351 121 army personnel deployed to the Persian Gulf during the Gulf War (August 1990 to March 1991). Of these veterans, 80 were determined to have died in the Gulf and were excluded from this analysis, leaving a total of 351 041 (Figure 1). Among these veterans, 100 487 were considered exposed and 224 980 were considered unexposed. Exposure could not be determined for 25 574 veterans, because of missing or invalid unit or service date information.

Exposure Determination

The 1997 plume model, the first model used to determine the potential for exposure to agents released at Khamisiyah, was developed by a joint team of Department of Defense and Central Intelligence Agency personnel. This model is described in detail on a Department of Defense Web site[7] and in a study assessing postwar morbidity of potentially exposed veterans.[6] The 1997 plume model used data collected from those who were present at the Khamisiyah demolitions and from reconstructed demolitions. Dispersion models were used to predict the transport and spread of chemical warfare agents according to simulated meteorologic conditions. The result was the generation of a simulated potential hazard area that varied in size and shape from March 10 to March 13, 1991. In 2000, the Department of Defense and the Central Intelligence Agency



Note. COD = cause of death. Exposure is based on the 2000 plume exposure model developed by the US Department of Defense.

FIGURE 1—Deaths identified through 2000 for exposed, unexposed, and exposure-unknown veterans who were present at the 1991 Khamisiyah chemical munitions destruction.

developed the 2000 plume model, a refined version of their 1997 model. The 2000 plume model is described by the Department of Defense on its Gulf War–related Web site. Our study relied on the 2000 model to determine the likelihood of exposure. The 2000 plume model includes several improvements over the 1997 model. Among the improvements are revised meteorologic models, a reduced amount of nerve agent released, the addition of cyclosarin toxicity data, and the deposition and degradation data. Another improvement is more precise information regarding the location of individual units in Iraq at the time of the 1991 demolitions. In the 1997 model, an individual's location was largely determined by the location of that person's battalion, whereas, in the 2000 model, an individual's location was determined by the company's location. Because a battalion consists of 500 to 900 soldiers and a company consists of only 100 to 200 soldiers, locating individuals at the company level is believed to be more precise than locating them at the battalion level. Unit locations were based on 855 000 recorded daily unit locations in the Gulf Theater. The extent to which this represents all locations for military personnel during the war is unknown.

Vital Status Determination and Cause of Death Data

Vital status follow-up for each veteran began on the date the veteran left the Gulf Theater alive and ended on the earlier of either the veteran's date of death or December 31, 2000. Follow-up ended on December 31, 2000, as sources used for vital status ascertainment were incomplete after that date. Vital status was ascertained in part using the Department of Veterans Affairs computer database known as BIRLS (Beneficiary Identification and Records Locator Subsystem). BIRLS identifies all veterans who are eligible for benefits, including death benefits. Veterans were also matched against a file of deaths reported to the Social Security Administration. An earlier study assessing the mortality of Gulf War veterans determined that when used together, the BIRLS and Social Security Administration files of deaths had an estimated reporting rate of 89% for Gulf-era veterans (95% confidence interval [CI]=83%, 97%).[3] Cause of death data were obtained from the National Death Index.

Military Service and Demographic Characteristics

Demographic and military service characteristics for each veteran were obtained from a Defense Manpower Data Center database. This database identifies military personnel who were serving in the Persian Gulf during the Gulf War. Available data included age, race, gender, dates of service, rank, unit component, unit name, unit identification code, and military occupational specialty code. In addition to exposure data (yes/no/unknown), the model also provided the number of days exposed, ranging from 1 to 4 days, and the days on which each veteran was in the plume footprint.

Statistical Methods

Unadjusted relative risks were calculated as crude death rates, with the numerator equal to the number of deaths and the denominator equal to the number of person-years a person is at risk of dying. Follow-up began on the date when a veteran left the Gulf Theater alive and ended on December 31, 2000, or the date of death, whichever came first. Adjusted relative risks (RRs) were calculated with standard SAS software for the Cox proportional hazards model to account for possible confounding and effect modification by selected covariates.[9] Covariates included exposure (yes or no), age at entry to follow-up, gender, race (White vs non-White), rank (enlisted vs officer or warrant officer), and unit component (active duty vs National Guard or Army Reserves). Cause-specific mortality risks were also calculated for those exposed 1 day and those exposed 2 or more days, each compared with all unexposed veterans. Finally, cause-specific mortality of exposed and unexposed veterans was compared with that of the US population with adjustment for age, race, gender, and calendar year.[10] The results were expressed as standardized mortality ratios (SMRs), or the ratio of observed deaths among veterans to the expected number of deaths as determined by the US population. Cause-specific mortality categories included all major diagnostic groupings as set forth in the *International Classification of Diseases, Ninth Revision (ICD-9)*.[11] Although many specific diagnoses were analyzed, only a few are presented in tabular form here. Any relative risk was considered statistically significant when its 95% CI did not include 1.00.

RESULTS

We identified 1179 deaths among exposed veterans, 2696 deaths among unexposed veterans, and 341 deaths among those with missing exposure data (Figure 1). Cause of death was obtained for 1133 (96%) of the deaths among exposed veterans, 2553 (95%) of the deaths among unexposed veterans, and 313 (92%) of those with missing exposure data. The majority of exposed, unexposed, and exposure-unknown veterans were White (64.8%, 64.5%, and 65.9%, respectively) and male (89.3%, 90.9%, and 86.9%, respectively) (Table 1). For all 3 groups, the majority of non-Whites, 81% to 82%, were African Americans, followed by Hispanics, 14.8% to 15%. The average age in years at entry to follow-up was 27.7 for exposed, 27.2 for unexposed, and 28.2 for exposure-unknown veterans. All veterans served in the army, and most were of the enlisted ranks: 88.4% of exposed, 89.8% of unexposed, and 86.7% of exposure-unknown veterans. Finally, 85.7% of exposed veterans were exposed for only 1 day.

Table 2 compares the overall and cause-specific mortality of exposed veterans with that of unexposed veterans, adjusting for age at entry to follow-up, race, gender, unit component, and rank. The overall mortality of both exposed and unexposed veterans was the same (RR=0.97; 95% CI=0.91, 1.04). Exposure was also not associated with an increased risk in disease-related mortality (*ICD-9* 001–799) (RR=0.96; 95% CI=0.86, 1.07). When we looked at specific diseases as well as major disease groupings, there was only 1 disease for which exposed veterans were at a statistically increased risk. Compared with unexposed veterans, exposed veterans had an almost twofold increased risk of brain cancer–related deaths (*ICD-9* 191, 192) (RR=1.94; 95% CI=1.12, 3.34). Although not presented in Table 2, other cause-specific deaths, both traumatic and disease-related, were examined; none were associated with exposure.

The mortality of veterans exposed 1 day and that of veterans exposed 2 or more days was compared separately with the mortality of all unexposed veterans, with adjustment for age at entry to follow-up, gender, race, rank, and unit component (Table 3). Neither those exposed 1 day nor those exposed 2 or more days were at increased risk for overall mortality when compared with all those unexposed (RR=0.97 and RR=0.96, respectively). The only increased risk in cause-specific mortality among exposed veterans was for brain cancer deaths. Compared with all unexposed veterans, the greater increased risk for brain cancer deaths among exposed veterans was for those exposed 2 or more days (RR=3.26; 95% CI=1.33, 7.96), whereas those exposed 1 day had a relative risk of 1.72 (95% CI=0.95, 3.10). A test of trend analysis indicated that the risk of brain cancer increases steadily as the length of exposure increases. With the exception of 4 days, a category consisting of 112 individuals, none of whom were brain cancer deaths, brain cancer death rates per 100 000 persons steadily increased with increased length of exposure: 0 days (unexposed)=11.97; 1 day=22.05; 2 days=39.83; and 3 days=60.35. A regression analysis of these data yields an estimate of 12.2 additional deaths per 100 000 persons for each added day of possible exposure (95% CI=4.8, 19.7).

We also compared the cause-specific mortality of all unexposed veterans, all exposed veterans, and exposed veterans when stratified by the number of days exposed (1 day or 2 or more days) with that of the

TABLE 1— Khamisiyah, Iraq, 1991 Chemical Munitions Destruction Exposure Status for US Army Gulf War Veterans, by Selected Demographic and Service Characteristics

	All Exposed (n = 100 487), No. (%)	All Unexposed (n = 224 980), No. (%)	Exposure Unknown (n = 25 574), No. (%)[a]
Age in 1990			
≤21	23 421 (23.3)	56 509 (25.1)	4951 (19.4)
22–25	25 825 (25.7)	58 852 (26.2)	6795 (26.6)
26–31	24 364 (24.2)	54 982 (24.4)	6302 (24.6)
≥32	26 877 (26.8)	54 637 (24.3)	7526 (29.4)
Mean age in 1990, y	27.7	27.2	28.2
Race			
White	65 146 (64.8)	145 009 (64.5)	16 849 (65.9)
Non-White	35 341 (35.2)	79 971 (35.5)	8725 (34.1)
Gender			
Male	89 777 (89.3)	204 594 (90.9)	22 225 (86.9)
Female	10 710 (10.6)	20 386 (9.1)	3349 (13.1)
Rank			
Enlisted	88 802 (88.4)	202 093 (89.8)	22 161 (86.7)
Warrant officer	1862 (1.8)	4728 (2.1)	703 (2.7)
Officer	9823 (9.8)	18 159 (8.1)	2710 (10.6)
Unit Component			
Active	74 464 (74.1)	175 089 (77.8)	17 745 (69.4)
Guard	11 897 (11.8)	24 445 (10.9)	1011 (3.9)
Reserve	14 126 (14.1)	25 446 (11.3)	6818 (26.7)
Number of days exposed			
1	86 167 (85.7)		
2	12 551 (12.5)		
3	1657 (1.7)		
4	112 (0.1)		

Note. Exposure is to nerve gas as a result of weapons demolition. Exposure is based on the 2000 exposure model developed by the US Department of Defense.
[a]Exposure status could not be determined because of missing or invalid unit data.

TABLE 2—Cause-Specific Mortality Among Exposed US Army Gulf War Veterans at Khamisiyah, Iraq, in 1991 Compared With Unexposed Army Veterans

Underlying cause of death (*ICD-9*)	Exposed (n = 100 487), No. (Rate[a])	Not Exposed (n = 224 980), No. (Rate[a])	Relative Risks: Crude	Relative Risks: Adjusted[b]	95% CI
All causes	1179 (12.22)	2696 (12.47)	0.98	0.97	0.91, 1.04
All diseases (001–799)	496 (5.14)	1093 (5.05)	1.02	0.96	0.86, 1.07
Infectious and parasitic disease (001–139)	29 (0.30)	56 (0.26)	1.16	1.16	0.74, 1.82
Malignant neoplasm (140–208)	184 (1.91)	391 (1.81)	1.06	0.97	0.82, 1.16
Colon cancer (153)	14 (0.15)	26 (0.12)	1.25	1.17	0.61, 2.25
Pancreatic cancer (157)	10 (0.10)	24 (0.11)	0.91	0.82	0.39, 1.73
Lung cancer (162)	30 (0.31)	84 (0.39)	0.80	0.72	0.47, 1.10
Brain cancer (191,192)	25 (0.26)	27 (0.12)	2.17	1.94	1.12, 3.34
Disease of circulatory system (390–459)	170 (1.76)	407 (1.88)	0.94	0.89	0.74, 1.06
Disease of respiratory system (460–519)	22 (0.23)	45 (0.21)	1.10	1.03	0.62, 1.72
Disease of digestive system (520–579)	24 (0.25)	46 (0.21)	1.17	1.10	0.67, 1.81
All external causes (E800–E989)	637 (6.60)	1460 (6.75)	0.98	1.01	0.92, 1.10
All accidents (E800–E929)	348 (3.61)	807 (3.73)	0.97	0.99	0.87, 1.12
Motor vehicle accident (E810–E929)	239 (2.48)	546 (2.52)	0.98	1.00	0.86, 1.17
Suicide (E950–E959)	174 (1.80)	386 (1.78)	1.01	1.05	0.88, 1.25

Note. ICD-9 = International Classification of Diseases, Ninth Revision; CI = 95% confidence interval. Exposure is to nerve gas as a result of demolition of weapons at Khamisiyah, Iraq. Exposure is based on the 2000 exposure model developed by the US Department of Defense.
[a]Crude death rates per 10 000 person-years at risk.
[b]Estimates of relative risk were derived from a proportional hazards multivariate model, with adjustment for age at entry to follow-up, race, sex, rank, and unit component.

US population, with adjustment for age, gender, race, and calendar year of death. The overall mortality for all 4 groups of veterans was less than half that expected as determined by the US population; the standardized mortality ratio for all exposed was 0.40 (95% CI=0.38, 0.42); the mortality ratio for those exposed 1 day was 0.40 (95% CI=0.38, 0.43); the mortality ratio for those exposed 2 or more days was 0.40 (95% CI=0.34, 0.47); and the mortality ratio for all unexposed veterans was 0.42 (95% CI=0.40, 0.43). When we looked at cause-specific mortality, the only excess we found in cause-specific deaths among all groups of exposed veterans was brain cancer deaths. The largest excess of brain cancer deaths among exposed veterans was among those veterans exposed 2 or more days (SMR=2.13; 95% CI=0.78, 4.63). Those veterans exposed 1 day also had an excess of brain cancer deaths, but it was not statistically significant (SMR=1.05; 95% CI=0.63, 1.64). All unexposed veterans had a standardized mortality ratio for brain cancer deaths of 0.71 (95% CI=0.46, 1.04).

Exposure Misclassification

To assess potential effects of exposure misclassification, we conducted several sensitivity tests. In order for chemical exposure in Khamisiyah to no longer be associated with a statistically significant increased risk of brain cancer death, a minimum of 3 exposed brain cancer deaths would have to be reclassified as unexposed, yielding a relative risk of 1.64 (95% CI=0.95, 2.85). Changing the length of exposure of 1 brain cancer death from 2 or more days to 1 day also had little effect on the relative risk for 2 or more days of exposure (RR=2.71; 95% CI=1.03, 7.09). Even after we reclassified 3 brain cancer deaths from veterans exposed 2 or more days to veterans exposed only 1 day, the length of exposure remained significantly associated with the risk of brain cancer death.

Finally, assigning 7% of veterans with missing exposure data to first exposed and then unexposed groups and recalculating relative risks of brain cancer (RR=1.70; 95% CI=1.00, 2.90; and RR=1.97; 95% CI=1.16, 3.36, respectively) did not produce relative risks dissimilar to that reported in Table 2 (RR=1.94).

Smoke Exposure

Another potentially harmful exposure that could have affected a large number of Gulf War veterans was exposure to smoke from oil well fires.[12] To assess the extent of oil well smoke exposure, we added 3 different measures of smoke exposure data to the model cited in Table 2. The 3 different measures of smoke exposure were (1) the number of days of modeled exposure multiplied by the average concentration of total suspended particulate (TSP); (2) the number of days at TSP level of 0.260 mg/m^3 or more times the average concentration of TSP level for those days; (3) the presence or absence of TSP exposure of 0.260 mg/m^3 or greater. We limited these supplemental analyses to veterans with at least 1 day of modeled TSP exposure (n=284 885). The 3 supplemental models yielded the following relative risk estimates of brain cancer deaths associated with Khamisiyah exposure: (1) relative risk was 2.25 (95% CI=1.12, 4.11), (2) relative risk was 2.30 (95% CI=1.26, 4.20), and (3) relative risk was 2.33 (95% CI=1.28, 4.25). None of these differ substantially from the original estimate of relative risk (RR=1.94; 95% CI=1.12, 3.34). To further assess the effects of exposure to smoke from oil well fires, we reran the models excluding the variable for Khamisiyah. None of the smoke exposure variables were associated with a statistically significant increased risk of brain cancer deaths.

Diagnostic Misclassification

In general, the accuracy of death certificates in determining cause of death is variable, especially regarding cancer-related deaths.[13,14] To determine which of the reported brain cancer deaths were most likely because of primary brain tumors, medical records were requested for all brain cancer deaths. Of the 55 brain cancer deaths, supplementary medical records were obtained for 42 veterans. A neurologist (R.T.J.; see Acknowledgments) who was blinded to

TABLE 3—Cause-Specific Mortality Risks Among US Army Gulf War Veterans Exposed at Khamisiyah, Iraq, in 1991 Stratified by Number of Days Exposed Compared With Unexposed Gulf War Veterans

Underlying Cause of Death *(ICD-9)*	1 Day Exposure (n = 86 167) No. (Rate[a])	≥ 2-Day Exposure (n = 14 320) No. (Rate[a])	All Nonexposed (n = 224 980) No. (Rate[a])	1-Day Exposure, RR[b] (95% CI)	≥ 2-Day Exposure, RR[b] (95% CI)
All causes	1020 (12.34)	159 (11.51)	2696 (12.47)	0.97 (0.90, 1.04)	0.96 (0.82, 1.13)
All diseases (001–799)	427 (5.17)	69 (5.00)	1093 (5.05)	0.95 (0.85, 1.06)	1.06 (0.83, 1.36)
Infectious and parasitic disease (001–139)	24 (0.29)	5 (0.36)	56 (0.26)	1.11 (0.69, 1.80)	1.49 (0.59, 3.74)
Malignant neoplasm (140–208)	156 (1.89)	28 (2.03)	391 (1.81)	0.94 (0.78, 1.13)	1.25 (0.85, 1.84)
Brain cancer (191, 192)	19 (0.23)	6 (0.43)	27 (0.12)	1.72 (0.95, 3.10)	3.26 (1.33, 7.96)
Disease of circulatory system (390–459)	147 (1.78)	23 (1.67)	407 (1.88)	0.88 (0.73, 1.07)	0.94 (0.61, 1.43)
Disease of respiratory system (469–519)	18 (0.22)	4 (0.29)	45 (0.21)	0.97 (0.56, 1.67)	1.58 (0.56, 4.42)
Disease of digestive system (520–579)	21 (0.25)	3 (0.22)	46 (0.21)	1.11 (0.66, 1.87)	1.02 (0.32, 3.31)
All external causes (E900–E989)	550 (6.65)	87 (6.30)	1460 (6.75)	1.01 (0.92, 1.12)	0.95 (0.77, 1.18)
All accidents (799–E929)	308 (3.73)	40 (2.90)	807 (3.73)	1.02 (0.89, 1.16)	0.79 (0.58, 1.09)
Motor vehicle accident (E810–E929)	213 (2.58)	26 (1.88)	546 (2.52)	1.04 (0.89, 1.22)	0.77 (0.52, 1.15)
Suicide (E950–E959)	142 (1.72)	32 (2.32)	386 (1.78)	1.00 (0.83, 1.21)	1.29 (0.90, 1.86)

Note. ICD-9 = *International Classification of Diseases, Ninth Revision;* RR = adjusted relative risk; CI = 95% confidence interval. Exposure is to nerve gas as a result of demolition of weapons at Khamisiyah, Iraq. Exposure is based on the 2000 exposure model developed by the US Department of Defense.
[a]Crude death rates per 10 000 person-years at risk.
[b]Estimates of relative risk were derived from a proportional hazards multivariate model, with adjustment for age at entry to follow-up, race, sex, rank, and unit component.

exposure status reviewed all available records to determine which deaths were because of primary gliomas. Of the original 55 brain cancer deaths, 47 were determined to be from primary brain tumors: 21 were from exposed subjects, 23 were from unexposed subjects, and 3 were from subjects with missing exposure data. Limiting brain cancer deaths to the 44 confirmed brain cancers with known exposure status, the risk of brain cancer death associated with chemical exposure in Khamisiyah was calculated with a proportional hazards model with adjustment for age at entry to follow-up, race, gender, rank, and unit component. Comparing exposed to unexposed veterans yielded an almost twofold statistically significant increased risk of brain cancer death associated with chemical exposure in Khamisiyah (RR = 1.88; 95% CI = 1.04, 3.41), virtually the same estimate as in Table 2. When we used only the 44 confirmed brain cancers, the relative risk estimate for those exposed 1 day was 1.66, and for those exposed 2 or more days, the RR estimate was 3.25.

Latency Analysis

The study's 10-year follow-up was divided into 3 follow-up periods of approximately equal length: original entry to follow-up to January 31, 1994 (follow-up 1); February 1, 1994, to July 31, 1997 (follow-up 2); and August 1, 1997, to December 31, 2000 (follow-up 3). For each follow-up period, an adjusted relative risk was calculated using the Cox proportional hazards model with adjustment for age, race, gender, unit component, and rank. The adjusted relative risks and number of exposed and unexposed brain cancer deaths for each follow-up period were as follows: in period 1, 6 exposed veterans and 7 unexposed veterans with brain cancer deaths—relative risk was 1.80 (95% CI = 0.60, 5.36); in period 2, 5 exposed veterans and 10 unexposed veterans with brain cancer deaths—relative risk was 0.99 (95% CI = 0.34, 2.91); and in period 3, 14 exposed veterans and 10 unexposed veterans with brain cancer deaths, relative risk was 3.03 (95% CI = 1.34, 6.82).

DISCUSSION

We compared the overall and cause-specific mortality of US Army Gulf War veterans potentially exposed to low-level chemical agents at Khamisiyah to that of US Army Gulf War veterans not exposed to chemical agents. When the mortality of all exposed veterans was compared with that of all unexposed veterans, with adjustment for covariates, there were no statistically significant differences between exposed and unexposed veterans except for an increased risk of brain cancer deaths among exposed veterans (RR = 1.94; 95% CI = 1.12, 3.34). Veterans exposed 2 or more days had a larger relative risk of brain cancer deaths (RR = 3.26; 95% CI = 1.33, 7.96) than veterans exposed only 1 day (RR = 1.72; 95% CI = 0.95, 3.10) when both were compared with unexposed veterans.

When we looked at the possibility of exposure misclassification, we found that 3 or more brain cancer deaths in exposed veterans would have to be reclassified as deaths in unexposed veterans to materially affect our results. Changing 3 of the 6 brain cancer deaths in exposed veterans from deaths in veterans exposed 2 or more days to deaths in veterans exposed 1 day did not alter the conclusion of the analysis of the length of exposure and risk of brain cancer death. Adding subjects with missing exposure data to either the exposed or unexposed cohort also did not materially change the results. Finally, adding data indicating exposure to smoke from oil well fires did not alter the original findings. Other potentially harmful exposures were present in the Gulf, but any of these exposures should be nondifferential regarding exposure as determined by the 2000 exposure model. As neither sarin nor cyclosarin are known carcinogens, it is possible that the demolitions at Khamisiyah may have involved additional agents or chemicals that were related to the increased risk of brain cancer death. The lack of data on pre- or post-Khamisiyah environmental or occupational exposures is also a shortcoming. When we examined the possibility of diagnostic misclassification, we found that limiting analysis to the 44 confirmed gliomas did not materially change the results.

When we looked at typical risk factors for brain cancer, we found that a Poisson regression model for brain cancer found the same risk factors—increased age, male gender, higher social class (here military rank)—that have been found in other studies,[15] except that there were no differences by race. Because there were no female brain cancer deaths, separate analyses could not be done by gender; however, Cox models such as those used in Table 2 were run separately for Whites and non-Whites. Although the risk of brain cancer deaths associated with Khamisiyah was higher among non-Whites than Whites (RR=3.14 vs RR=1.59, respectively), the confidence intervals overlapped. Reported environmental and occupational risk factors for brain cancers are few and are believed to account for only a small proportion of all brain cancer deaths. Ionizing radiation is one such factor.[15] Among the occupational groups reported to be at increased risk for adult brain tumors are petrochemical workers,[16] electrical workers and those exposed to electromagnetic waves,[17,18] and those exposed to agrochemicals.[19]

Despite the apparent robustness of this study's finding of an association between brain cancer death and possible exposure to chemical warfare agents, a certain measure of caution is needed in its interpretation. First, until quite recently there has been little evidence suggesting that subacute exposure to chemical warfare agents could cause any health effects at all.[2] However, recent animal studies reported alterations in the brain that could lead to memory loss and cognitive dysfunction[20] and sarin-induced immunosuppression.[21]

The short latency period suggested by this study is contrary to the reported latency period of tumors. The brain tumors from this study would at most have a latency period of 10 years if they were related to some exposure at Khamisiyah. Research on brain cancers associated with occupational exposure, specifically exposure to radiofrequency fields from cell phones, report a latency period of 10 to 20 years.[22] The same latency period characterizes most other cancers. However, a recent study of brain tumors among a group of young military radar operators reported a latency period of less than 10 years.[23] Cancers such as leukemia and multiple myeloma have reported latency periods of 2 to 3.5 years between exposure and death.[24]

We found an approximately twofold excess of brain cancer deaths, 12 to 13 excess deaths in a population of 100 000 veterans, associated with possible exposure to chemical warfare agents. This finding was adjusted for the effects of age, race, gender, rank, and unit component and was robust to the potential effects of exposure and diagnostic misclassification, as well as latency; the addition of data on exposure to smoke from oil well fires also had no material effect on this result. Moreover, although the data were very sparse, risk increased monotonically with the number of days of possible exposure. Although considerable caution is warranted in the interpretation of this finding, we suggest that further follow-up of this and other possibly exposed military cohorts be undertaken. ■

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Contributors

T.A. Bullman conducted the analyses and prepared the article. W.F. Page originated the study, supervised its progress, and coordinated data retrieval. C.M. Mahan provided assistance with data analysis. H.K. Kang participated in the origination and design of the study and provided administrative and material support. All authors reviewed drafts of the study, contributed to critical revision of the article, and provided assistance in all other aspects of study.

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